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Review article

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A guide to uraemic toxicity

Griet Glorieux [1] ✉, Stéphane Burtey [2], Pieter Evenepoel [3], Joachim Jankowski [4,5], Laetitia Koppe [6,7], Rosalinde Masereeuw [8] & Raymond Vanholder [1]

Abstract

When kidney function is compromised, myriad metabolites and peptides — uraemic retention molecules (URMs) — accumulate in the body and compromise homeostasis. Over 150 molecules have been classified as URMs but omics approaches are revealing many more. When URMs exert pathophysiological effects and/or are associated with relevant adverse patient outcomes, they are called uraemic toxins. The origins of uraemic toxins and their contributions to post-translational modification of proteins are important current areas of research. Although most research has thus far focused on uraemic toxins, new studies have also identified URMs with the potential to counteract harmful biological changes that might thus confer a beneficial effect. To tackle the growing burden of chronic kidney disease, preventive therapeutic measures must target the disease early in its course and a balanced view of uraemic retention is needed to understand the role of URMs in kidney disease progression. Knowledge of the origin of the solutes, their kinetics, context-dependent biological profile and the involvement of transporter-mediated interorgan communication by small molecules — termed 'remote sensing and signalling' — is indispensable to facilitate the development of interventions that can promote or restore homeostasis in people with kidney dysfunction.

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[1]Department of Internal Medicine and Pediatrics, Nephrology Section, Ghent University Hospital, Ghent, Belgium. [2]Faculty of Pharmacy, Aix Marseille University, INSERM, INRAE, Marseille, France. [3]Department of Microbiology, Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, KU Leuven, Leuven, Belgium. [4]Institute for Molecular Cardiovascular Research, Medical Faculty, RWTH Aachen University, Aachen, Germany. [5]Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, The Netherlands. [6]CarMeN Laboratory, INSERM, INRAE, Claude Bernard Lyon 1 University, Pierre-Bénite, France. [7]Department of Nephrology and Nutrition, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France. [8]Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands. ✉e-mail: griet.glorieux@ugent.be

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Key points

- Uraemic retention molecules, which accumulate as kidney function declines, are key mediators in the pathophysiology of chronic kidney disease.
- Uraemic retention molecules can be deleterious for the whole organism (termed uraemic toxins) but can also have beneficial effects.
- Identification of uraemic toxin receptors and downstream affected signalling pathways is key to understanding their pathological effects and developing targeted therapeutic strategies.
- Chronic kidney disease is associated with alterations in protein post-translational modifications, which can transform physiological molecules into mediators of pathology.
- Various promising therapeutic approaches to reducing uraemic toxicity, including drug therapy, nutritional approaches, new dialysis membrane materials, as well as bioartificial and wearable artificial kidneys, are currently being investigated.

Introduction

One key function of the kidneys is their ability to cleanse plasma of metabolic waste products. A decline in this function — for example, in the context of kidney disease — leads to metabolite retention, which can disrupt homeostatic processes. Functional abnormalities that are often associated with kidney diseases irrespective of the primary cause, including cardiovascular abnormalities, hypertension, sarcopenia and increased susceptibility to infection and malignancies, are largely attributable to the accumulation of these metabolic waste products[1]. Consequently, kidney disease often exacerbates the adverse outcomes associated with comorbid conditions such as diabetes and cardiovascular disease[2,3]. Additionally, metabolite retention is associated with distressing symptoms such as fatigue and itching[4]. Although these symptoms might not affect outcomes such as mortality directly, they generate stress and affect personal, social and family life considerably, with a potential indirect effect on hard clinical outcomes. Thus, kidney disease occupies a central position within a complex network of other conditions, imposing a considerable burden on clinical outcomes and quality of life (Fig. 1).

Consequently, the health of individuals who are affected by kidney dysfunction deteriorates progressively throughout the disease course. For example, cardiovascular risk doubles when kidney clearance drops below 50% normal capacity and this risk increases even earlier if albuminuria is slightly elevated (>30 mg/g creatinine). Accordingly, cardiovascular risk is several hundredfold higher in young individuals undergoing dialysis compared with an age-matched general population[5–7]. Importantly, most symptoms of kidney disease manifest only in advanced stages of the disease, which, coupled with inadequate screening and treatment, results in irreparable kidney damage, earning kidney disease the label of 'silent killer'[8]. In the interval of time between the onset of kidney dysfunction and its detection, all body systems can be affected, potentially irreversibly.

The understanding that kidney diseases are linked to elevated concentrations of various metabolites has evolved with advances in analytical techniques. Over time, it became clear that such elevated metabolite levels could alter biological functions with important clinical implications. This 'guide to' Review article summarizes the current knowledge on metabolite retention in kidney disease and its consequences, emphasizing the scientific rationale for developing strategies that can mitigate these effects.

Classification of uraemic toxins

The term uraemia originates from urea, which is the metabolite that accumulates most abundantly in kidney dysfunction. The collection of symptoms and complications associated with uraemia is termed uraemic syndrome. Molecules that are typically excreted by healthy kidneys into urine but are retained in cases of kidney dysfunction are termed uraemic retention molecules (URMs). URMs must fulfil several criteria to be classified as uraemic toxins (UTs)[9]. First, solute identification and accurate quantitative analysis in plasma, serum or blood must be possible, as their levels should be higher in people with chronic kidney disease (CKD) than in individuals without CKD. Moreover, negative effects conforming with or contributing to biological or clinical changes observed in CKD, should be proven in vivo, ex vivo or in vitro. Finally, biologically active concentrations in these studies should conform to those found in plasma, serum or blood of people with CKD.

The term uraemia first appeared in the title of a medical article[10] in 1861, but nearly a century passed before uraemic toxicity garnered similar attention[11,12]. The middle molecule hypothesis represents one of the seminal conceptual advances, suggesting that numerous pathogenic molecules were retained in kidney dysfunction[13]. The observation that individuals treated with peritoneal dialysis had less polyneuropathy than those receiving haemodialysis, which at that time primarily removed molecules with a molecular weight <500 Da, led to the hypothesis that larger molecules — which were termed 'middle molecules' — had a pathological role. When this hypothesis was proposed, little was known about the identity of these molecules. However, this understanding rapidly expanded with the development of dialysis membranes with larger pores[14] and the almost simultaneous detection of β_2-microglobulin (molecular weight ~12,000 Da) deposition in dialysis-related amyloidosis[15]. Protein-bound molecules were linked to kidney dysfunction around the same period[16] but their clinical relevance did not gain prominence until much later[17].

The prevailing classifications of UTs rely primarily on the extent to which they are removed by dialysis. The initial URM classification published in 2003 categorized these molecules into three groups[18]: small water-soluble molecules with a maximum molecular weight of 500 Da (easily eliminated by all dialysis methods); protein-bound molecules, also predominantly with a molecular weight below 500 Da (challenging to remove through dialysis owing to their binding to protein); and middle molecules, which are mostly small peptides with a molecular weight > 500 Da (best removed using large-pore dialysers such as high-flux dialysers).

Using this classification scheme, an initial comprehensive 2003 review by the European Uremic Toxin Workgroup (EUTox) categorized 90 URMs[19]. A 2012 update incorporated 56 newly reported molecules[20]. The surge in metabolomic and proteomic analyses over the past two decades has further expanded the detection range of both identifiable and non-identifiable molecules[21]. An analysis of ten untargeted metabolomic studies, which focused on the detection of molecules associated with relevant outcomes of CKD, revealed a low yield of toxic compounds[22]. This low yield might be partly attributed to the potential for positive or negative effects of retrieved molecules, as well as the lack of information regarding the biological effect of many

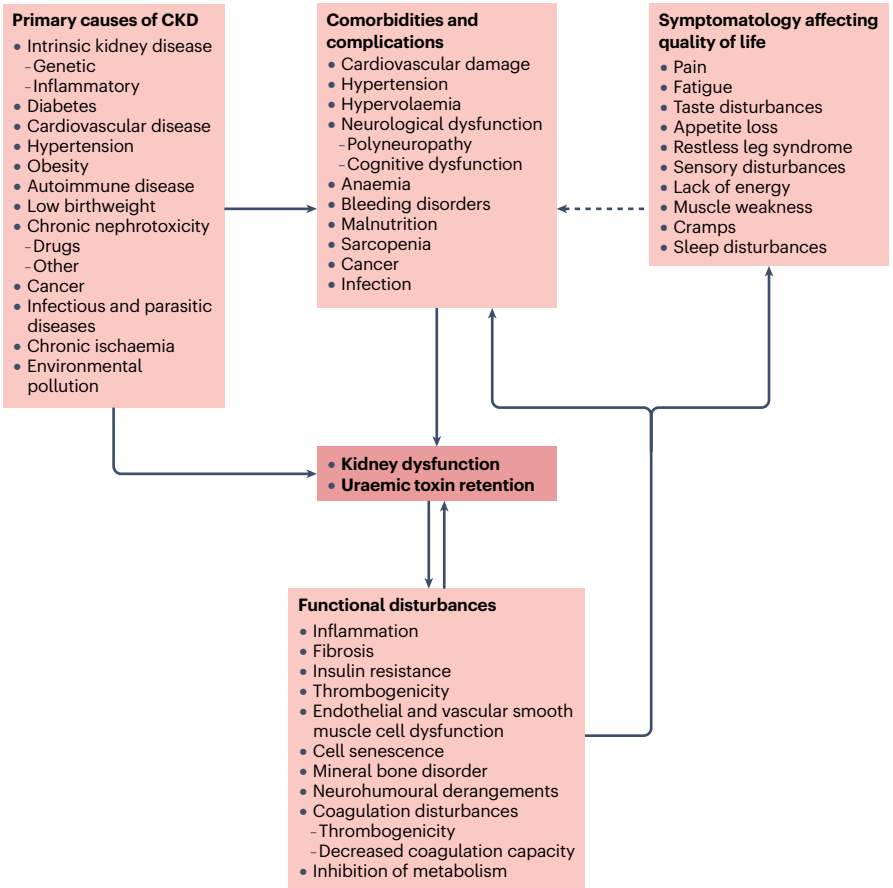


Fig. 1 | Pathophysiological changes with a central role in kidney dysfunction and uraemic toxin retention. A variety of primary causes might underlie kidney dysfunction, which results in uraemic toxin retention that can lead to functional changes, in turn leading to complications and symptoms affecting quality of life. The chronic kidney disease (CKD)-associated symptom burden might not affect hard clinical outcomes such as survival directly, but can have indirect effects, including stress induction, that can exacerbate the negative impact of CKD. Complications can accelerate the negative outcomes of comorbidities (for example, sleep disorders can further promote CKD-associated metabolic dysfunction and cognitive decline). Both functional changes and complications can also accelerate the progression of kidney dysfunction.

molecules. For example, two studies found only one molecule associated with CKD outcomes, but a toxic effect has not been reported[23,24]. Nonetheless, untargeted metabolomics offer a more balanced view of the retention process than targeted approaches[22], underscoring the fact that enzyme and microorganism metabolism leading to UT formation often also generates beneficial compounds. In addition, untargeted metabolomics sometimes enables the detection of unidentified UTs (as was the case for trimethylamine-*N*-oxide (TMAO)[25]) or of an unknown association with clinical effects (such as the link between TMAO levels and progression of kidney insufficiency[26] or cognitive dysfunction[27], and between phenyl sulfate levels and the progression of albuminuria in diabetes[28]). Consequently, continued metabolomic analysis in CKD is warranted, if the methodology adheres to current recommendations[22], particularly in combination with currently available information and/or new experimental studies on identified molecules to investigate potential toxicity.

Inspired by advances in dialytic removal strategies and membrane polymer chemistry, a more granular extension[9] of the 2003 classification[18], comprising six subclasses, was introduced in 2021. Alongside the existing classes of small water-soluble and protein-bound molecules, the middle molecule category was divided into small, medium and large middle molecules. Additionally, a new class of large molecules was introduced, with a molecular weight above the 58,000-Da cut-off of the glomerular sieve. Although it can be assumed that kidney dysfunction does not affect the concentration of those molecules because even healthy glomeruli cannot clear them, they are still regarded as potential UTs, given that kidney dysfunction leads to their post-translational modification (PTM) to generate biologically active molecules (for example, through carbamylation, glycosylation or guanidinylation) with pathological potential[29,30].

Importantly, dialysis is only used in a small fraction of individuals with kidney dysfunction, and such classifications therefore fail to consider changes in metabolite concentrations at earlier stages of the disease, which are affected, for example, by nutrition and gut microbial metabolism, as well as glomerular and tubular clearance function. The limitation of these classifications argues for the need for an alternative approach that also considers UTs early on in the development of CKD and can inform strategies to maintain homeostasis[31,32] (Fig. 2).

Origin of uraemic toxins

UTs originate from three primary sources (Table 1). They can be host-derived (products of metabolism that accumulate as kidney function declines); dietary-derived (molecules or their precursors that are ingested, absorbed and sometimes further metabolized in the body); or of microbial origin (precursors are metabolized by the gut microbiota with the resulting metabolites being subsequently absorbed)[33]. Of note, to acknowledge the large effect of the gut microbiome on mammalian blood metabolites[34], humans are often referred to as 'supraorganisms' or holobionts.

Intestinal microbial metabolism produces both toxic and beneficial molecules. This duality is exemplified by tryptophan metabolism, which generates UTs such as indoxyl sulfate (IxS) and kynurenines,

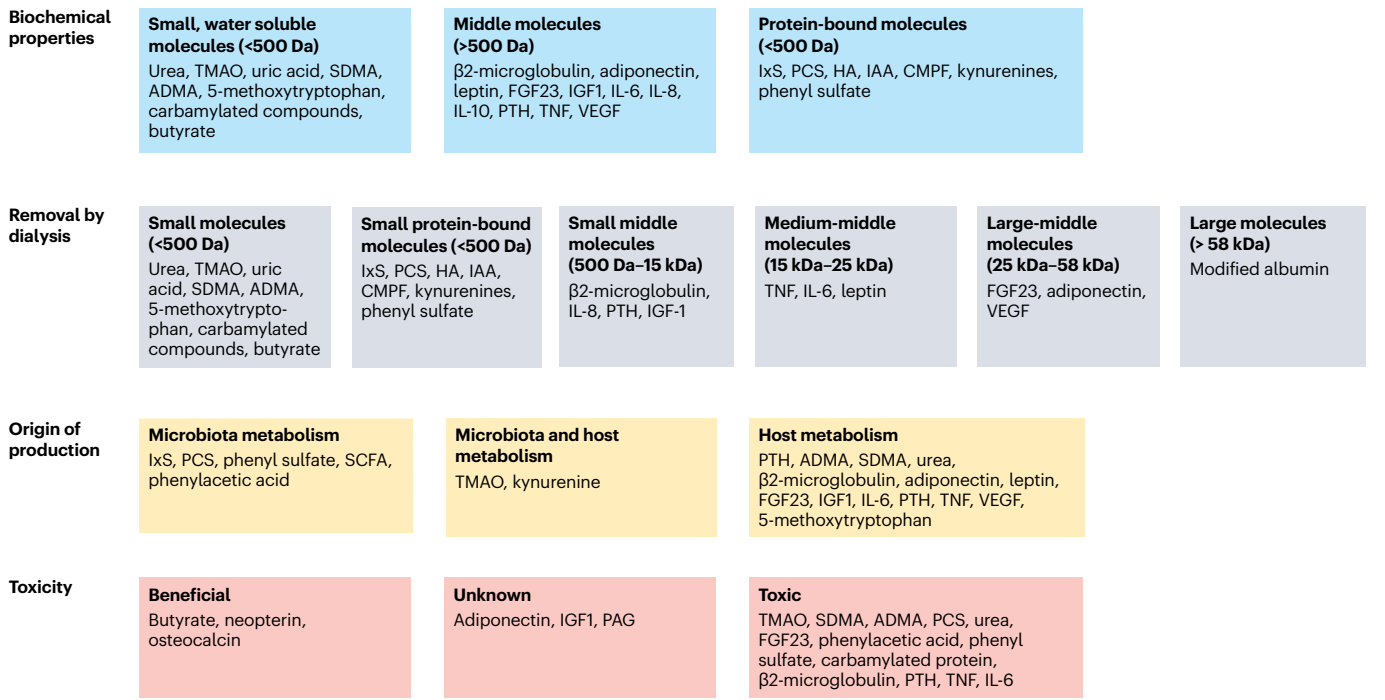

Biochemical properties
Small, water soluble molecules (<500 Da)
Urea, TMAO, uric acid, SDMA, ADMA, 5-methoxytryptophan, carbamylated compounds, butyrate
Middle molecules (>500 Da)
β2-microglobulin, adiponectin, leptin, FGF23, IGF1, IL-6, IL-8, IL-10, PTH, TNF, VEGF
Protein-bound molecules (<500 Da)
IxS, PCS, HA, IAA, CMPF, kynurenines, phenyl sulfate
Removal by dialysis
Small molecules (<500 Da)
Urea, TMAO, uric acid, SDMA, ADMA, 5-methoxytrypto-phan, carbamylated compounds, butyrate
Small protein-bound molecules (<500 Da)
IxS, PCS, HA, IAA, CMPF, kynurenines, phenyl sulfate
Small middle molecules (500 Da–15 kDa)
β2-microglobulin, IL-8, PTH, IGF-1
Medium-middle molecules (15 kDa–25 kDa)
TNF, IL-6, leptin
Large-middle molecules (25 kDa–58 kDa)
FGF23, adiponectin, VEGF
Large molecules (> 58 kDa)
Modified albumin
Origin of production
Microbiota metabolism
IxS, PCS, phenyl sulfate, SCFA, phenylacetic acid
Microbiota and host metabolism
TMAO, kynurenine
Host metabolism
PTH, ADMA, SDMA, urea, β2-microglobulin, adiponectin, leptin, FGF23, IGF1, IL-6, PTH, TNF, VEGF, 5-methoxytryptophan
Toxicity
Beneficial
Butyrate, neopterin, osteocalcin
Unknown
Adiponectin, IGF1, PAG
Toxic
TMAO, SDMA, ADMA, PCS, urea, FGF23, phenylacetic acid, phenyl sulfate, carbamylated protein, β2-microglobulin, PTH, TNF, IL-6

Fig. 2 | Classification of uraemic retention molecules. In addition to the classical classification of uraemic retention molecules based on their biochemical properties and whether they can be removed by dialysis, uraemic toxins can also be classified according to their origin and toxicity. Solutes with a beneficial effect have the potential to counteract harmful biological changes associated with the progression of chronic kidney disease. A more balanced view of uraemic retention is needed to enable the development of interventions that can support the maintenance, or restoration, of homeostasis. ADMA, asymmetric dimethylarginine; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; FGF, fibroblast growth factor; HA, hippuric acid; IAA: indole acetic acid; IGF-1, insulin-like growth factor-1; IxS, indoxyl sulfate; PAG, phenylacetylglutamine; PCS, *p*-cresyl sulfate; PTH, parathyroid hormone; SCFA, short-chain fatty acid; SMDA, symmetric dimethylarginine; TNF, tumour necrosis factor; TMAO, trimethylamine-*N*-oxide; VEGF, vascular epithelial growth factor.

alongside beneficial compounds such as indole and indole–propionic acid (IPA)[35]. This phenomenon extends beyond tryptophan metabolites and is evident across various aspects of human metabolism in uraemia, including the interplay between pro- and anti-inflammatory cytokines and the dual outcomes of aryl hydrocarbon receptor (AHR) activation (discussed below).

Remote sensing and signalling

Nigam and coworkers[36] have proposed the existence of a 'remote sensing and signalling network', whereby numerous transporter proteins, enzymes, and membrane and nuclear receptors interact to establish communication across organisms and organs[37] (Fig. 3). Under physiological conditions, body homeostasis is largely maintained by remote sensing and signalling, which requires a network of genes and proteins involved in absorption, distribution, metabolism and excretion of metabolites along the gut–liver–heart–brain–kidney metabolic axis[35] (Fig. 3). As key regulators of homeostasis, the kidneys can sense changes in metabolite concentrations, particular via olfactory receptors, taste receptors, the erythroblastic leukaemia viral oncogene homologue (ERBB) family of receptor tyrosine kinases[38] and other sensory G-protein-coupled receptors expressed in different regions of the nephron[39]. An in vitro uptake assay in transfected cells demonstrated that olfactory receptor ligands can inhibit transport mediated by organic anion transporter 6 (OAT6) and/or OAT1, suggesting that olfactory receptors and transporter proteins might function in parallel in homeostasis regulation owing to their ability to respond to the same or similar ligands[40]. Notably, the kidney clearance of various drugs in CKD is also dependent on OAT activity, and might compromise transport and excretion of other substrates (including uraemic metabolites) in patients treated, for example, with angiotensin receptor blockers and furosemide[41–43]. However, clearance of uraemic metabolites is not restricted to OAT expression and activity, as the proximal tubule also expresses an organic cation transporter (OCT2) and the organic anion transporting polypeptide (OATP4C1), both of which are responsible for the uptake of UTs[44–47], as well as efflux transporters[42] (Fig. 3a). Furthermore, a decrease in the expression of kidney transporter proteins has been reported in animal models of both acute kidney injury and CKD. This reduction compromised their capacity to secrete UTs and contributed to their accumulation and toxic effects. These changes are not limited to CKD but might also occur in other comorbidities. Reduced OAT3 was observed in an animal model of obesity[48], and both OAT1 and OAT3 were decreased in animal models of diabetic kidney disease[49] compared with controls. In the liver, IxS is associated with an increase in P-glycoprotein (P-gp; ABCB1) expression, potentially necessitating an increased posology of cyclosporin, a P-gp substrate, to achieve target concentrations in people with a functioning kidney or heart transplant receiving this drug as part of their immunosuppressive regimen[50]. These findings underscore the importance of the OAT system in resilience against stress and injury, and the effect of uraemia on excretory transport systems.

Notably, when kidney function starts to decline, remote sensing and signalling triggers mechanisms that can compensate for the decreased removal of metabolites. This compensatory effect has been described for uric acid, whereby UT accumulation triggers an increase in the expression and/or function of the intestinal transporter breast cancer resistance protein (BCRP; *ABCG2*), which eliminates uric acid from the blood through excretion into the intestinal lumen[51]. The same mechanism has also been suggested to promote intestinal secretion of IxS[52,53]. Furthermore, a high plasma concentration of IxS is sensed by a concerted action of the epidermal growth factor receptor (EGFR) and AHR, leading to an increased expression of OAT1 in kidney proximal tubular cells to enhance the excretion of IxS and other UTs that depend on this transporter[54]. In addition, in a mouse model of CKD associated with a high concentration of IxS, the expression of the two enzymes that convert indole to IxS — cytochrome P450 (CYP)2E1 and sulfotransferase (SULT)1A1 — was reduced, suggesting a feedback mechanism to reduce the concentration of IxS[55]. Compensatory expression of OATP4C1 was also observed in double *Oat1* and *Oat3* knockout rats[56]. Although dietary protein intake, which is linked to increased generation of amino acid-derived UT precursors, has been demonstrated to remotely modulate the excretion of IxS by increasing tubular transporter expression, the potential effects of dietary changes and drug therapy on human compensatory mechanisms remain unclear[57].

In CKD, remote sensing and signalling has a role in determining UT concentration through metabolism, not only in the kidney but also in the liver (Fig. 3a). These compensatory and/or regulatory mechanisms can initially help to maintain or restore homeostasis. However, as soon as the balance has tipped, owing to chronic accumulation of metabolites, remote sensing and signalling might become harmful, as it affects various biological processes and systems with a potentially damaging effect.

Uraemic toxicity

Uraemic toxicity arises from the retention of numerous known or as yet unidentified molecules. An in-depth exploration of uraemic toxicity mechanisms is beyond the scope of this Review, but here we provide a concise overview of UTs for which strong clinical and experimental toxicity evidence is available. Rather than present an exhaustive list of UTs, we illustrate the diversity and multifaceted attributes of uraemic toxicity and its multi-organ impact. We first describe several well-accepted toxic effects for each toxin[58–63] (Table 1), followed by a discussion of the latest toxicity data.

Urea

Urea is a metabolite derived from nitrogen-containing molecules present in the body and in food. Once considered inert, urea is now linked to key toxic effects, including inflammation, insulin resistance, cell death and disruption of the intestinal barrier[62]. Urea has also been implicated in disruption of the blood–brain barrier[64], which might have a role in the reported association between urea and CKD-related anxiety[65] or depressive symptoms[66]. A study of over a million US veterans showed that higher levels of urea were associated with an increased risk of incident diabetes independent of glomerular filtration rate (GFR)[67]. Furthermore, urea is a predictor of cardiovascular outcomes independently of other known cardiovascular risk factors, including estimated GFR (eGFR)[68]. Inhibition of the urea transporter by dimethylthiourea in a CKD mouse model reduced hypertension and cardiac fibrosis, and improved heart function according to echocardiographic evaluation[69]. The pathological role of carbamylated compounds[70], which are derived from the dissociation of urea, is discussed below, under PTMs.

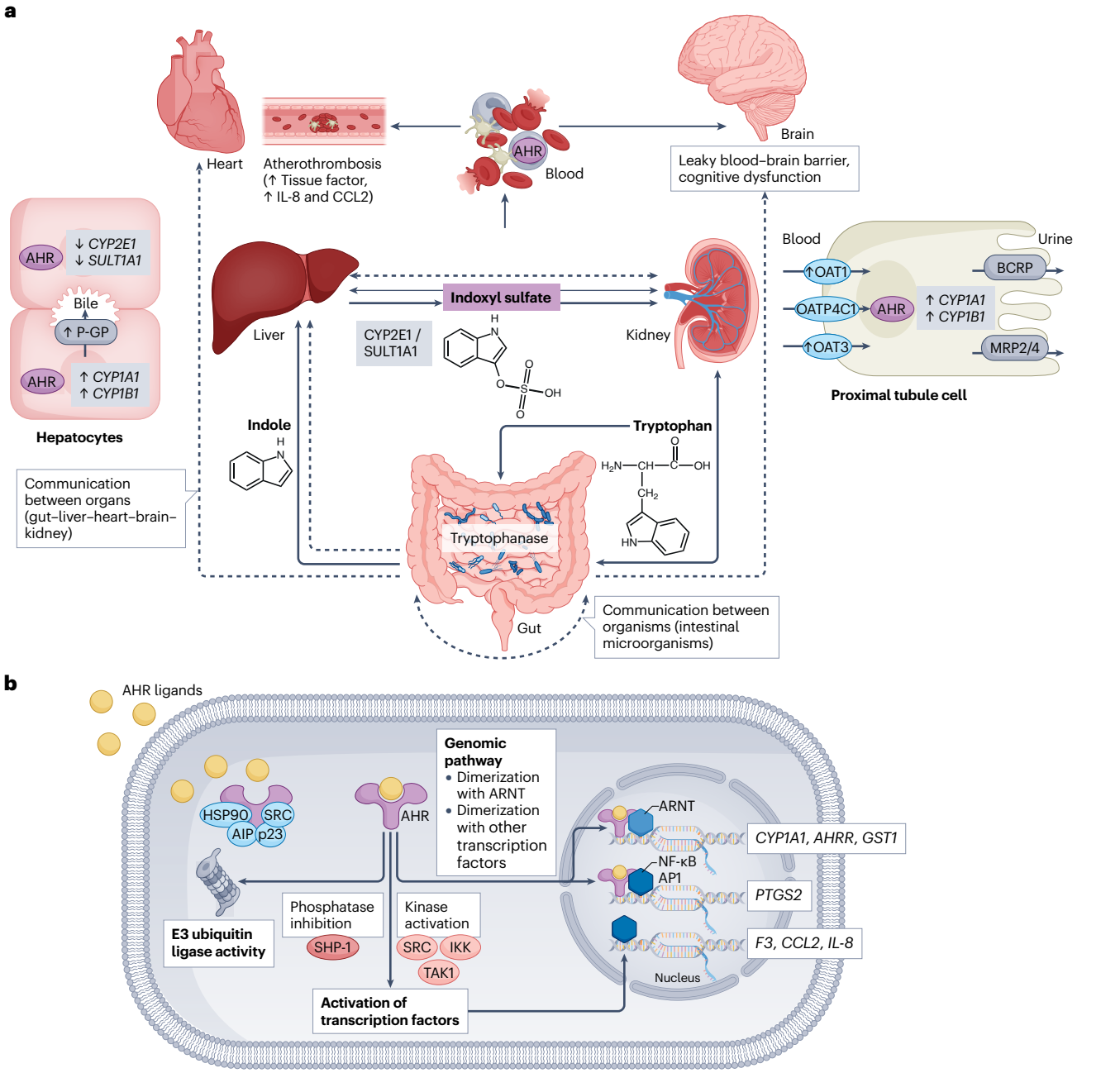
Uric acid

Uric acid is a metabolite derived from nucleic acids originating from the body and diet, and has been associated with inflammation and insulin resistance, as well as vascular and kidney damage[63]. A J-shaped non-linear relationship between serum uric acid and all-cause and cardiovascular mortality was observed in people with CKD[71]. However, pharmacological treatment with allopurinol to lower uric acid levels, either alone[72,73] or in combination with the uric acid transporter 1

Table 1 | The origin and toxic effects of the main uraemic toxins

Uraemic toxin	Origin	Main effects
Small water-soluble molecules		
Urea	Host Diet	Inflammation Insulin resistance Cell death Intestinal wall disruption
Uric acid	Host Diet	Inflammation Vascular damage Insulin resistance Kidney damage
ADMA	Host	Endothelial dysfunction Cardiovascular damage Oxidative stress Neurotoxicity
SDMA	Host	Endothelial damage Inflammation
Protein-bound molecules		
p-Cresyl sulfate	Microbial	Oxidative stress Endothelial damage Kidney fibrosis Insulin resistance
Indoxyl sulfate	Microbial	Inflammation Vascular damage Fibrosis Kidney dysfunction Insulin resistance
Kynurenines	Host	Thrombogenicity Inflammation Cognitive dysfunction Inhibition drug metabolism
Middle molecules		
β_2-Microglobulin	Host	Bone and joint amyloidosis Erythrocyte damage Inflammation Cognitive dysfunction
FGF23	Host	Cardiac hypertrophy Vascular damage Inhibition neutrophil response
IL-6	Host	Inflammation Cachexia

ADMA, asymmetric dimethylarginine; FGF23, fibroblast growth factor-23; PTH, parathyroid hormone; SDMA, symmetric dimethylarginine.



inhibitor verinurad[74], did not reduce albuminuria or slow eGFR decline in people with CKD and hyperuricaemia.

Asymmetric dimethyl arginine

Asymmetric dimethyl arginine (ADMA) is a by-product of arginine metabolism that has not only been associated with endothelial dysfunction and cardiovascular damage but also contributes to inflammation and neurological alterations[63]. Elevated ADMA levels might be an early predictor of albuminuria and of CKD progression in people with hypertension, or with hypertension and diabetes[75]. ADMA is also a novel risk factor for coronary artery calcification progression in people with CKD[76].

Symmetric dimethyl arginine

Symmetric dimethyl arginine (SDMA) is a structural isomer of ADMA and is also an arginine metabolite; it has been implicated in endothelial damage and pro-inflammatory effects[63]. In people with CKD not receiving dialysis, SDMA levels can be used to predict CKD progression and future atherosclerotic cardiovascular events more consistently than other methylarginines[77]. In people with acute coronary syndrome receiving dual antiplatelet therapy, SDMA is associated with lower platelet reactivity, and with major and minor bleeding events[78]. SDMA can also predict the presence of atrial fibrillation and, in vitro, rapid pacing leads to increased symmetric protein methylation and elevated SDMA in induced pluripotent stem-cell-derived cardiomyocytes[79].

Fig. 3 | Remote sensing and signalling, and the role of metabolism and transport of indoxyl sulfate. a, In the intestine, bacterial tryptophanase degrades tryptophan into indole, which is absorbed and metabolized in the liver by cytochrome P450 (CYP)2E1 and sulfotransferase (SULT)1A1, resulting in the end-product indoxyl sulfate (IxS). In the kidneys, IxS is secreted by proximal tubular cells via the influx transporters organic anion transporter 1 (OAT1), OAT3 and organic anion transporting polypeptide 4C1 (OATP4C1), and the efflux transporters multidrug resistance-associated proteins 2 (MRP2), MRP4 and breast cancer resistance protein (BCRP). Accumulation of IxS in chronic kidney disease (CKD) leads to activation of the aryl hydrocarbon receptor (AHR). As a physiological response to this IxS accumulation, expression of CYP2E1 and SULT1A1 in the liver decreases, whereas OAT1 and OAT3 expression increases. These changes decrease the generation IxS while enhancing its clearance from the blood, partly attenuating the deleterious effects of AHR activation in blood vessels, which are known to contribute to atherothrombosis through activation of coagulation (expression of tissue factor) and inflammation (expression of IL-8 and CC-chemokine ligand 2 (CCL2; also known as monocyte chemoattractant protein-1 (MCP1)). AHR activation increases blood–brain barrier permeability, which is associated with brain dysfunction and cognitive dysfunction. However, activation of AHR can also have beneficial effects via the activation of detoxification pathways, such as CYP1A1 and CYP1B1 or P-glycoprotein (P-gp) in the liver. Remote sensing and signalling pathways between organisms and organs are mediated by small molecules that regulate metabolism. The proteins mediating these effects include transporters, metabolizing enzymes and membrane and nuclear receptors. **b**, AHR is a transcription factor that controls various signalling pathways. At rest, AHR is retained in the cytoplasm in a complex composed of heat shock protein (HSP)90, AHR-interacting protein (AIP), protein (p)23 and SRC. After binding its ligands, AHR is released from the complex and can act as a transcription factor. First, it might dimerize with AHR nuclear translocator (ARNT) in the nucleus, initiating a genomic pathway that leads to the expression of genes related to detoxification (*CYP1A1*, *AHRR* and *GST1*). AHR can also dimerize with other transcription factors, such as subunits of nuclear factor-κB (NF-κB) or AP1, leading to the expression of inflammatory genes such as *PTGS2*. Moreover, AHR can modulate the phosphorylation of transcription factors by inhibiting phosphatases or kinase activation; this inflammatory pathway (or non-genomic pathway) leads to the expression of genes involved in inflammation and thrombosis such as *F3*, *CCL2* and *IL8*. Finally, AHR can also function as an E3 ubiquitin ligase.

p-Cresyl sulfate

p-Cresyl sulfate (pCS) is a microbial metabolite of tyrosine and phenylalanine. Its toxicity arises from pro-inflammatory effects that contribute to vascular damage[59]. Additionally, it has been associated with kidney fibrosis, potentially accelerating the progression of kidney dysfunction[59]. pCS also contributed to intracellular reactive oxygen species production and lipid peroxidation in adipose cells through activation of NADPH oxidase[80]. In vitro, pCS-induced ROS-triggered epithelial–mesenchymal transition, stress fibre redistribution and migration in a bladder cancer cell line[81]. pCS contributes to endothelial dysfunction[82], compromises cardiac structure and function by reducing klotho and SIRT6 expression and increasing cell apoptosis in neonatal rat cardiomyocytes[83], and inhibits autophagic flux in endothelial cells[84]. In a rat model of CKD, pCS promotes vascular calcification via induction of hyperglycaemia and insulin resistance, which contributes to activation of inflammation and coagulation pathways[85]. Furthermore, pCS might contribute to immune dysfunction by decreasing peripheral B cell numbers through inhibition of proliferation of $CD43^+$ B cell progenitors observed in mouse bone marrow[86]. Among other protein-bound UTs (PBUTs), free pCS has the highest association with cardiovascular outcomes in people with CKD not receiving dialysis[87] and this association is not explained by albumin levels[88].

Indoxyl sulfate

One of the most frequently studied URMs, IxS, is a product of tryptophan metabolism linked to numerous adverse effects, including inflammation, endothelial damage, fibrosis and insulin resistance[61]. Its effects on insulin resistance, inflammation and coagulation pathways have also been linked with vascular calcification[85]. In addition, IxS also increased the expression of the hepatic transporter P-gp, thus affecting drug clearance[50]. Further studies showed that IxS promoted platelet hyperactivity with thrombus formation[89], hepcidin expression with deregulation of iron metabolism[90], tubular epithelial cell senescence[91] and myoblast apoptosis contributing to sarcopenia[92]. Finally, IxS has also been implicated in epileptic seizure development[93], cognitive dysfunction and blood–brain barrier alterations[94,95], colorectal cancer exacerbation[96] and ovarian cancer cell metastasis[97]. Most of these effects occur via AHR activation (see below).

Kynurenines

Kynurenines are a group of metabolites that also derive from tryptophan and are traditionally associated with prothrombotic effects via AHR activation[63]. Additional roles for these metabolites include pro-inflammatory effects, cognitive dysfunction and inhibition of drug metabolism[95]. Much of the latest evidence implicating kynurenines in pathological processes has been indirect – for example, based on induced dysbiosis that increases kynurenine generation, but might also alter the production of other metabolites – creating uncertainty regarding the specific contribution of kynurenines[98]. Nonetheless, novel proposed roles for kynurenines include the initiation of endothelial dysfunction and damage[99], cardiomyocyte damage through apoptosis and autophagy[100], and neuro-inflammation, with potential promotion of brain-cell death, neuron loss and axon demyelination, as well as exacerbation of multiple sclerosis[101].

FGF23

Fibroblast growth factor-23 (FGF23) is a large polypeptide and middle molecule that is crucial to calcium–phosphorus homeostasis; its activities are closely linked to those of parathyroid hormone (PTH)[60]. In addition to their role on bone physiology, both hormones mainly affect the cardiovascular and immune systems[63]. However, whereas the relationship between FGF23 and mortality is straightforward[102], that of PTH is biphasic, with both low and high PTH linked to increased mortality[103]. FGF23 has been implicated in cardiac hypertrophy and failure, vascular damage and impaired neutrophil responses, with potentially enhanced susceptibility to infection[60]. The latest experimental data on FGF23 essentially corroborates its cardiovascular and immunological effects. Elevated FGF23 is associated with mitochondrial dysfunction preceding the development of cardiomyocyte hypertrophy[104], promotion of cardiac fibrosis[105,106], endothelial injury through nuclear factor (NF)-κB activation[107] and phenotypic changes of vascular smooth muscle cells that promote vascular stiffening and wall thickness[108]. Immune-response inhibition was confirmed in a study showing that pre-treatment with FGF-23 weakened neutrophil chemotaxis in microfluidic devices[109].

β_2-Microglobulin

β_2-Microglobulin is a small polypeptide derived from the breakdown of major histocompatibility complex class I (MHCI)[63]. Accumulation

Box 1 | The complex layering of uraemic toxicity

Origin of uraemic toxins
- Diet
- Endogenous mammalian (host) metabolism
- Microbial metabolism

Cause of shifts in metabolization
- Uraemia
- Diet
- Drug therapy

Effect on metabolite concentrations
- Generation
- Absorption
- Elimination

Multicompartmental distribution
- Circulatory levels might not reflect cellular and tissue levels

Duality of functional impact of metabolites and their receptor-mediated effects
- Toxic
- Neutral
- Beneficial

Counteracting interactions between molecules
- Cocktail effect
- Derangement of homeostasis

Post-translational modifications of molecules
- Functional changes
- Activity changes
- Changes in receptor binding

Therapeutic approaches
- Lack of selectivity (toxins versus beneficial molecules)
- Poor removal of protein-bound uraemic toxins

of β_2-microglobulin following prolonged dialysis has been associated with bone and joint amyloidosis[63]. Once thought to be inert, later studies have linked β_2-microglobulin to altered erythrocyte rigidity, pro-inflammatory effects and neurotoxicity[63]. The latest studies on β_2-microglobulin have confirmed its neurotoxic role[110] and its effect on cognitive function, as well as a potential role in itching[111,112].

IL-6

IL-6 is a large polypeptide and cytokine with primarily pro-inflammatory effects that contributes to cachexia[58]. Overexpression of IL-6 in mice caused vascular dysfunction, leukocyte accumulation and fibrosis, and decreased survival[113]. IL-6 was also linked to postoperative atrial fibrillation through a signal transducer and activator of transcription 3 (STAT3)-driven ryanodine receptor-2 calcium leak[114]. In a placebo-controlled trial in people receiving haemodialysis, the anti-IL-6 antibody ziltivekimab decreased inflammation and resistance against erythropoiesis-stimulating agents[115]. Of note, IL-6 increases FGF23 transcription and contributes to the high levels of FGF23 observed in CKD[116]. Further interesting observations include changes in behavioural domains associated with several psychiatric disorders in pre-pubescent mice after IL-6 administration[117] and a considerable reduction in calcium-induced itching in IL-6-deficient mice[118].

The complex layering of uraemic toxicity

Uraemic toxicity affects whole organ systems, including the immune, cardiovascular and nervous systems[94], the kidneys and the skeleton[119]. Common pathways include increased oxidative stress[120], inflammation[121] and thrombogenicity[122], decreased neovascularization[123,124] and enhanced tissue remodelling[38]. All these processes involve complex signalling mechanisms that alert different parts of the body and can transform a physiological response into a pathological process (Box 1). To exert cellular toxicity, the candidate UT must be transported into the cell, which in many cases requires a specific transporter. IxS and pCS, for example, require the presence of an OAT to cause cellular toxicity. Toxicity might be direct and/or receptor-mediated; identification of UT receptors is important to identify the signalling pathways involved in uraemic toxicity.

Aryl hydrocarbon receptor. Many endogenous and microbial tryptophan catabolites activate AHR (Fig. 3). AHR is a member of the PER–AHR nuclear translocator (ARNT)–SIM (PAS) superfamily of transcription factors[125]. In the cytoplasm, AHR is contained in a protein complex composed of heat shock protein 90 (HSP90), AHR-interacting protein (AIP), co-chaperone p23 and the protein kinase SRC. After binding, and depending on the ligand, cell type and cellular environment, AHR can have three functions in cell signalling (Fig. 3b). The classical function involves the modulation of genomic pathways owing to a transcriptional factor role. In this case, AHR dissociates from its partners in the cytoplasm and moves to the nucleus where it binds to the ARNT. The AHR–ARNT dimer is recruited to xenobiotic response elements in the promoter region of target genes, leading to an increase in the expression of numerous genes encoding proteins involved in detoxification, such as cytochrome CYP1A1, CYP1B1, NAD(P)H:quinone acceptor oxidoreductases (NQO)1 or uridine glucuronosyltransferase (UGT)1A1. Overall, this transcriptional effect might be considered beneficial[126]. In the nucleus, AHR can also interact with other transcription factors, such as subunits of NF-κB, with a pro-inflammatory effect[127]. The second function of AHR is the control of ubiquitination. In the cytoplasm, AHR has an E3 ubiquitin ligase function, whereby it controls thrombotic risk mediated by tissue factor in vascular smooth muscle cells[128]. The third pathway of AHR signalling modulation is mediated by the level of phosphorylation of transcription factors. AHR activation can lead to the activation of kinases such as SRC, IKK, TAK1, MAPK or phosphatase-like SHP-1. This pathway mainly drives inflammation through the activation of NF-κB, leading to the expression of genes encoding tissue factor, prostaglandin-endoperoxide synthase 2 (PTGS2), IL-8 and CC-chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein-1 (MCP-1)). These changes in gene expression promote thrombogenicity and inflammation, which is deleterious to the cardiovascular system[129].

Of note, AHR also connects the microbiota, the immune system and metabolism. For example, in a mouse model of multiple sclerosis (specifically, experimental autoimmune encephalomyelitis), AHR loss in T cells induced microbiota alterations leading to increased apoptosis of T helper 17 (T_H17) cells via increased production of biliary salts;

clinical scores also improved[130]. AHR activation has the important role in gut health of controlling the response to gut inflammation mediated by bacteria. Defective activation of AHR is associated with active coeliac disease and AHR activation through modification of the microbiota in response to increased dietary tryptophan or direct administration of AHR ligands reduced the risk of coeliac disease in a mouse model[131]. Furthermore, loss of AHR in the endothelial capillaries of the gut leads to activation of the endothelium associated with an increased risk of death in a mouse model of gut infection[132].

AHR activation has a beneficial role in metabolic dysfunction-associated steatotic liver disease (MASLD) through its function as a regulator of the gut barrier[133]. By contrast, increased activation potential of AHR in the aorta and heart of CKD mice was suggested to be a key mechanism underlying increased cardiovascular risk[134]. Understanding the different molecular partners involved in these AHR activities could pave the way to identifying specific inhibitors of the inflammatory AHR pathway, providing new molecular targets to reduce thrombo-inflammation in CKD.

Uraemic toxin transporters and receptors. Targeting UT transporters and receptors is appealing to mitigate toxicity but might prove challenging, particularly because of lack of specificity. Both the ligand, exposure kinetics, and cell type might define the outcome of receptor activation[35], complicating uraemic toxicity research. In addition, uraemia can affect receptor expression, as observed, for example, with the PTH receptor[135].

Uraemic toxin metabolism. Mounting evidence indicates that increased circulating levels of a renally excreted metabolite are not always associated with a negative biological effect. Circulating metabolite levels reflect the balance between generation and elimination. Kidney disease might cause shifts in endogenous and microbial metabolism, with decreasing or increasing generation rates; uraemia, nutritional changes or drug therapy can drive these metabolic shifts. Metabolic shifts at the cellular and tissue level are poorly captured by circulating levels, particularly in the setting of kidney disease. A decreased generation rate translates into low circulating levels only in the absence of kidney retention and thus often remains unnoticed. However, metabolic shifts can prove as important as kidney retention in driving uraemic biological effects. CKD, for example, can promote a shift in microbial tryptophan metabolism from the beneficial IPA, towards indole production, which is a precursor of several harmful compounds[136], thus creating a pro-inflammatory environment[137]. IPA might be labelled a 'uraemic depletion metabolite' and its reduced concentration could be hypothesized to contribute to the uraemic syndrome as much as the accumulation of several classical URMs. Similarly, other tryptophan metabolites with a beneficial potential, such as melatonin[138] and nicotinamide[139], are decreased in advanced CKD.

In addition to its effect on the generation and elimination of metabolites, kidney disease can also alter the structure and function of proteins through enzymatic and non-enzymatic PTMs[30]. Post-translationally modified proteins can contribute to inflammation, oxidative stress and fibrosis, and induce vascular damage or prothrombotic effects, which might contribute to CKD progression and/or increase cardiovascular risk in people with CKD (discussed in detail below). These novel insights call for a broader view of uraemic toxicity, beyond kidney retention, which might unveil therapeutic options beyond blood purification[140].

Ascertaining toxicity. Importantly, toxicity is context dependent. Biological effects can depend on exposure kinetics (affecting, for example, UT concentrations or exposure duration) and might be cell, tissue or species specific. Metabolites can thus confer both harm or benefit, depending on the circumstances. This dualism and 'context dependency' are best documented for endogenous and microbial tryptophan metabolites[35]. For example, microbial tryptophan metabolites can confer benefits in the gastrointestinal microenvironment but might become toxic if they accumulate in the systemic circulation. This duality might also explain why some of these metabolites have been associated with both beneficial and harmful outcomes in experimental and clinical studies.

According to the classical definition, ~150 compounds currently qualify as UTs. The list is rapidly growing, partly owing to advances in metabolomics and proteomics[141]. Both bottom-up and top-down approaches have been adopted to identify UTs. Bottom-up approaches start with untargeted metabolomics (discovery), followed by targeted mass spectrometry analysis to quantify the URMs and confirmation using an independent (validation) cohort. Toxicity is subsequently explored in mechanistic studies[142–144]. In the top-down approach, the toxicity of well-established URMs is demonstrated in mechanistic studies and in clinical outcome studies. Both approaches have limitations and pitfalls, thus warranting cautious interpretation. Statistical flaws, such as residual confounding, preclude the use of prospective observational outcome studies to establish whether a URM is a true UT. For example, the association between a given compound and poor health outcomes could suggest direct toxicity but might also simply reflect a class effect related to the origin (metabolism) or kinetic characteristics of the molecule. For most potential UTs, the clinical impact can only be assessed through observational studies, which carries the risk of confounding with kidney function, particularly GFR. However, for some UTs, such as pCS conjugates, the association with health outcomes persists even after adjustment for eGFR[87]. One underlying reason might be that, particularly for protein-bound compounds and polypeptides, elimination might depend largely on tubular rather than glomerular function, and GFR does not necessarily reflect alterations in tubular function[145,146].

Currently, observational clinical assessment of uraemic toxicity is unavoidable, and corroboration of observational suggestions of toxicity through experimental data is therefore essential. Of note, experimental studies must also be interpreted with caution because, in addition to potential interspecies differences, exposure conditions and/or kinetics often mimic complex clinical settings poorly. The EUTox group has published recommendations for handling URMs in vitro to optimize comparability[147]. Finally, experimental UT research has thus far focused on single toxins or on selected panels of toxins. This approach oversimplifies the complex mutual interaction between UTs and other homeostatic derangements in vivo.

Randomized controlled clinical trials (RCTs) provide the highest level of evidence of toxicity but might be ethically unacceptable or practically unfeasible because a specific treatment is lacking. For the few toxins for which a concentration decrease is possible or suggested (for example, uric acid, homocysteine, pCS and IxS), RCT data were sometimes ambiguous[148,149], possibly because uraemia is not a single-toxin condition. Observational studies are easier to perform, but cannot offer absolute proof of causation, even if supported by extensive experimental data.

Post-translational modifications

In CKD, the accumulation of UTs results in the enhanced or dysregulated PTM of proteins, peptides and lipoproteins, owing to increased

concentrations of uraemic retention solutes, such as urea[150,151], guanidino compounds, such as creatinine, guanidine, guanidinosuccinate, dimethylarginines and methylguanidine[150,151], reactive carbonyl species[152,153] or hyperglycaemia[154,155]. These PTMs can alter the charge, conformation, localization and interactions of the biomolecules they modify, thereby disrupting a wide array of cellular processes and regulatory pathways[30]. CKD-associated PTMs can contribute to systemic inflammation, oxidative stress and vascular dysfunction. Furthermore, these modifications adversely affect key clinical outcomes, including the progression of CKD and deterioration of cardiovascular health. The identification of these modified proteins as potential biomarkers highlights their value in monitoring disease progression and guiding therapeutic strategies, as they might affect drug pharmacokinetics and therapeutic efficacy[156]. Understanding the specific PTMs involved also facilitates the development of novel therapeutic approaches to CKD and its cardiovascular complications to optimize treatment strategies and enhance patient management[157].

Identification of post-translational modifications

Only a subset of potential CKD-associated PTMs has been identified thus far. The development and application of advanced mass spectrometry-based techniques have been essential for comprehensively identifying these modifications[158]. High-resolution mass spectrometers, as well as nuclear magnetic resonance spectrometry, are crucial tools. Given the extensive array of UTs implicated in the induction of PTMs, several modifications are probably yet to be identified.

Alterations of biological functions by post-translational modifications

The biological functions of native proteins, peptides and lipoproteins can be diminished or completely altered by PTMs. Specific PTMs, especially carbamylation, guanidinylation and oxidation (Box 2), have been well-documented in people with CKD.

Carbamylation. In people with CKD, carbamylation is mainly induced by increased urea plasma concentrations[159–161]. This PTM induces structural and functional changes in the affected proteins that can disrupt normal cellular processes and contribute to the development of various pathological conditions[162], including cardiovascular disease and dysregulated protein homeostasis. Post-translational carbamylation of haemoglobin impairs its oxygen-binding capacity, compounding the anaemia commonly observed in people with CKD[163]. Carbamylation also affects the functional properties of albumin, reducing its ability to bind and/or transport molecules[164], including several hormones and common drugs, which can complicate clinical care. Moreover, carbamylation of HDL renders it pro-inflammatory, impairing its cholesterol efflux capacity and protective role in vascular health. In people with CKD, carbamylated HDL promotes endothelial dysfunction and inflammation, further increasing the risk of atherosclerosis and cardiovascular disease[165]. In the arterial wall, carbamylation affects structural proteins, such as collagen and elastin, reducing vascular elasticity and contributing to vascular stiffness, thus heightening the risk of hypertension and cardiovascular complications[30]. Of note, carbamylated albumin has been identified as a potential biomarker for increased mortality risk in people with CKD and kidney failure[162]. Overall, the presence of carbamylated proteins in CKD correlates with worse outcomes, including a higher risk of cardiovascular events, hospitalization and mortality[162].

Guanidinylation. Post-translational guanidinylation of apolipoprotein C3 (APOC3) or APOA1 caused by guanidine and urea[166,167] can occur in CKD, and high levels of guanidinylated APOC3 are associated with an increased risk of cardiovascular events and CKD progression[167,168]. This modification has been implicated in the dysregulation of lipid metabolism, exacerbating atherosclerosis and contributing to heightened inflammatory responses. Furthermore, guanidinylation alters the structural and functional properties of APOC3, potentially impairing its interaction with lipid-binding proteins and receptors. These findings suggest that guanidinylated APOC3 might serve as both a biomarker and a pathogenic mediator in the progression of cardiorenal diseases[167]. In addition, increased guanidinylation of fibrinogen can substantially alter fibrin clot achitecture[169]. Specifically, guanidinylation resulted in the formation of thinner fibrin fibres, with a reported ~30% reduction in fibre thickness compared with non-guanidinylated fibrinogen. This structural modification probably compromises the mechanical properties of the fibrin network, potentially impairing its stability and clotting efficiency. Alterations in fibrin architecture contribute to disrupted haemostatic function in people with CKD, particularly in the context of elevated levels of guanidine compounds, and further aggravate the elevated cardiovascular risk inherent to CKD by fostering abnormal clot formation and increasing the propensity for thrombotic events[169]. The accumulation of guanidine components in CKD also leads to changes in the

Box 2 | Origin of post-translational modifications in chronic kidney disease

Carbamylation: elevated circulating urea in chronic kidney disease (CKD) leads to an increase in levels of cyanate, which readily reacts with free amine groups of lysine residues and the N terminus of proteins, as well as free sulfhydryl groups, such as those in cysteine residues. These reactions result in the formation of carbamylated proteins, characterized by the covalent attachment of a carbamoyl group (–CONH2) to the protein structure.

Guanidinylation: guanidine compounds such as creatinine, guanidine, guanidinosuccinate and methylguanidine accumulate in people with CKD, promoting non-enzymatic protein guanidinylation of proteins, peptides and lipoproteins, which alters protein function[164].

Oxidation: the significantly increased oxidative stress caused by reactive oxygen species in people with CKD results in strong post-translational oxidation of proteins and lipoproteins. The most common oxidative modifications in CKD include carbonylation, sulfoxidation and nitrosylation[270]. Protein carbonylation, for instance, results from directly oxidizing amino-acid side chains, such as proline, arginine, lysine and/or threonine, introducing carbonyl groups into the protein structure[271,272]. Sulfoxidation occurs by forming sulfoxides and sulfinic acids, particularly of methionine and cysteine residues. Finally, lipoproteins, particularly LDL and HDL, are highly prone to oxidative modifications in CKD.

structural and functional properties of lipoproteins, particularly HDL[170]. HDL particles, which are typically anti-inflammatory and cardioprotective, become pro-inflammatory in the presence of guanidine compounds. This modified HDL contributes to increased oxidative stress and endothelial dysfunction, and promotes atherogenicity, thereby accelerating vascular damage. Furthermore, the shift towards a pro-inflammatory HDL phenotype has been strongly associated with poor clinical outcomes, including increased cardiovascular events and higher mortality rates[166,171]. These findings underscore the effect of guanidine compound-induced modifications in HDL in exacerbating cardiovascular and kidney complications in CKD, and highlight the importance of targeting these pathways for therapeutic intervention.

Oxidation. In CKD, an imbalance between oxidative and antioxidant signalling leads to excessive production of reactive species, which results in increased levels of reactive oxygen species[172], reactive nitrogen species and reactive carbonyl species, such as 4-hydroxy-2-nonenal (4-HNE) and 4-hydroxy-2-hexenal (4-HHE)[152,153]. These reactive molecules induce post-translational oxidation of proteins and lipoproteins, which has a crucial role in the pathophysiology of CKD. The oxidation of proteins and lipoproteins contributes significantly to the progression of CKD, particularly by exacerbating cardiovascular complications and disrupting cellular homeostasis, ultimately leading to organ dysfunction and increased morbidity. Post-translationally oxidized proteins and lipoproteins undergo structural and functional changes when interacting with ROS[173]. The accumulation of carbonylated proteins has been implicated in the deterioration of kidney function and the acceleration of atherosclerosis and vascular damage in CKD[174]. These modifications affect protein stability and enzyme activity, disrupting essential cellular functions. The oxidation of thiol groups in cysteine residues affects the redox regulation of proteins and enzymes, critical in maintaining cellular homeostasis and signalling pathways[175].

Oxidized LDL (ox-LDL) is a key driver of atherosclerosis, a major complication of CKD. LDL undergoes lipid peroxidation following exposure to ROS, forming oxidized phospholipids, aldehydes and malondialdehyde adducts[176]. These LDL particles can be recognized by macrophage scavenger receptors, which promotes foam-cell formation and the subsequent development of atherosclerotic plaques. Additionally, ox-LDL contributes to endothelial dysfunction by increasing the expression of adhesion molecules and pro-inflammatory cytokines. In CKD, clearance of ox-LDL from the circulation is impaired owing to reduced hepatic LDL receptor activity, exacerbating vascular damage[177,178].

HDL also undergoes oxidative modifications that significantly reduce its protective capacity. Oxidized HDL is less effective at promoting cholesterol efflux from macrophages, which leads to cholesterol build-up in the vascular walls[179]. Moreover, oxidized HDL loses its anti-inflammatory and antioxidant capacity, transforming it into a pro-inflammatory agent that further contributes to vascular injury and the progression of atherosclerosis[180,181].

Future investigations should focus on integrating PTM identification with functional studies to understand the effect of these modifications on disease pathogenesis. Advances in high-throughput proteomics, imaging techniques and computational modelling facilitate the characterization of PTMs and their effects on CKD. Exploring the interactions between different PTMs and their cumulative effect on disease progression will also provide a more comprehensive understanding of CKD pathology. Furthermore, developing therapeutic strategies to prevent or mitigate PTMs in CKD and avert their detrimental effects represents an urgent research need.

Prevention, lifestyle and treatment

To limit the effect of UTs, particularly PBUTs, therapeutic strategies focus on three main approaches: targeting the gut microbiota to reduce UT production, enhancing UT elimination and minimizing UT toxicity (Fig. 4). Maintaining a balance between beneficial gut metabolites, such as short-chain fatty acids (SCFAs) and certain indoles, and harmful gut-derived toxins remains a key challenge[182].

Pharmacological interventions and sorbents

In conventional treatment of CKD, progressive increases in UT levels are primarily addressed through medications such as renin–angiotensin–aldosterone system (RAAS) and sodium–glucose co-transporter 2 (SGLT2) inhibitors, which help to slow down the deterioration of kidney function[183]. Several preclinical and clinical studies also showed that SGLT2 inhibitors lower the production of microbiota-derived UTs, reducing systemic exposure to these toxins as well as the demand for their excretion in the kidneys[184]. This effect on gut structure and microbiota composition has mainly been demonstrated with canagliflozin-mediated inhibition of gastrointestinal SGLT1, which potentially influences the gut environment[185–188]. Although not fully explored, RAAS inhibitors might indirectly reduce the toxic effects of UTs; losartan significantly decreased nephrosclerosis caused by IxS and pCS[189]. Of note, people with CKD treated with various medications, such as phosphate and potassium binders, might experience gut microbiota changes, but their potential effect on UT levels remains unclear and varies across studies[190–192].

Given the key role of gut microbiota in producing UTs, several pharmacological strategies targeting the production or absorption of microbiota-derived UTs have been proposed for uraemia management. Proof-of-concept studies have shown that antibiotic therapy, colectomy or colonic irrigation can reduce levels of gut-derived UTs, although the clinical use of those strategies remains impractical[193–196]. Colonic transit time is an important factor in UT generation. Prolonged transit promotes a metabolic shift from carbohydrate fermentation to protein catabolism, potentially leading to increased levels of harmful protein-derived metabolites[197]. Constipation has been associated with a higher risk of kidney failure[198,199] and its prevalence increases with CKD progression, creating a vicious cycle that is further exacerbated by the use of phosphate binders and dietary-fibre restrictions in advanced disease stages[200]. Addressing constipation should therefore be an important therapeutic target. Experimental studies in CKD models have demonstrated that certain laxatives — such as lubiprostone (a ClC-2 chloride channel activator), lactulose and linaclotide (a guanylate cyclase-C agonist) — can beneficially modulate the gut microbiota, reduce PBUTs, and attenuate kidney inflammation and injury[201,202]. Faecal microbiota transplantation might also help to restore dysbiosis, but its high cost, side effects, probable short-term efficacy and, in some countries, legal restraints, limit its use in people with CKD[203].

Advances in materials science represent promising opportunities for therapies aimed at selectively adsorbing PBUTs or their precursors from the intestine. The first such therapy to be evaluated was AST-120, a spherical carbon adsorbent. Although preclinical data were promising, a large RCT did not show significant kidney protection[148]. However, in a post hoc analysis, AST-120 decreased CKD progression in the tertile

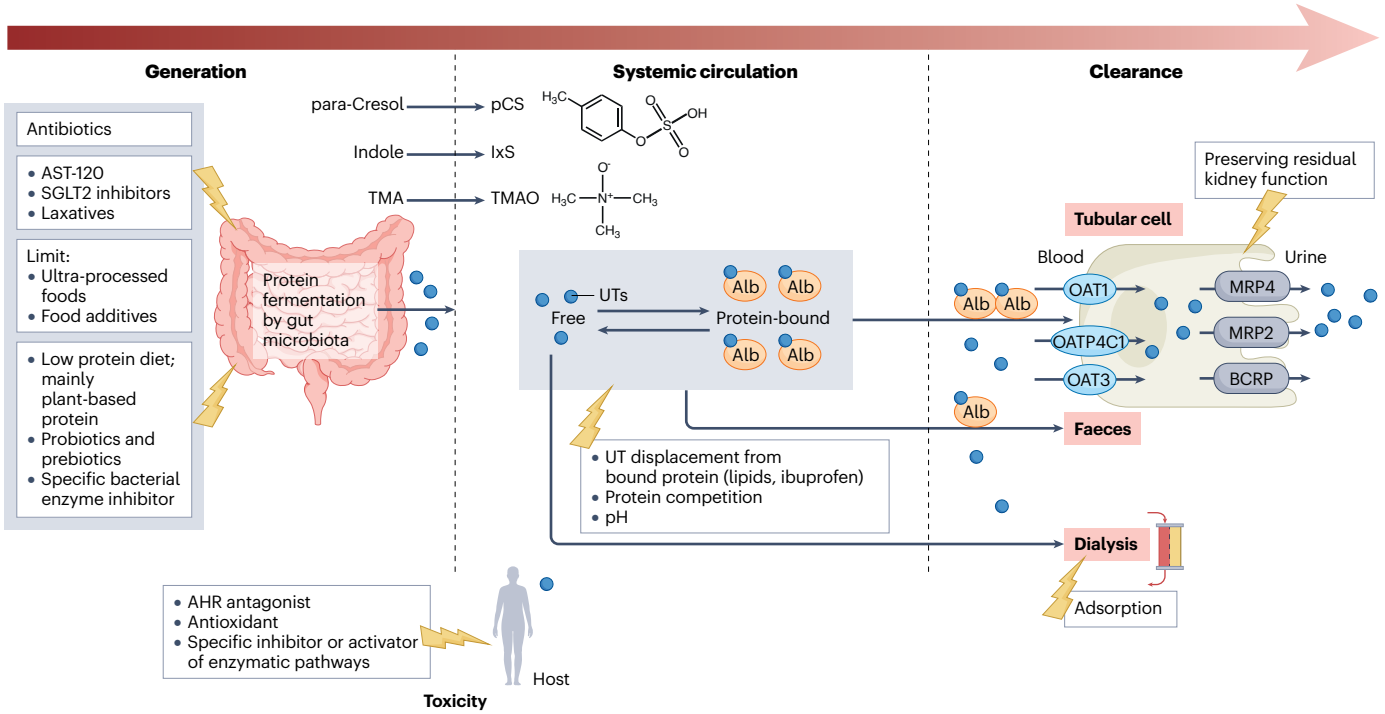


Fig. 4 | Therapeutic strategies to reduce uraemic toxin production, accumulation and toxicity. To limit the effect of uraemic toxins (UTs), particularly protein-bound UTs (PBUTs), such as *p*-cresyl sulfate (pCS) and indoxyl sulfate (IxS), therapeutic strategies focus on three main approaches: targeting the gut microbiota to reduce UT generation (for example, by using medication, diet and/or supplements); enhancing PBUT elimination (for example, by disrupting their binding to albumin (Alb), improving UT clearance by preserving residual kidney function and/or optimizing dialysis therapy), and minimizing toxicity (for example, through the administration of aryl hydrocarbon receptor (AHR) antagonists or antioxidants). BCRP, breast-cancer resistance protein; MRP2, multidrug resistance-associated protein 2; OAT, organic anion transporter; OATP4C1, organic anion transporting polypeptide 4C1; SGLT2, sodium–glucose co-transporter 2; TMA, trimethylamine; TMAO, TMA-*N*-oxide.

of patients with the highest IxS reductions[204]. A key challenge with AST-120 is its non-selectivity, owing to its large pore size distribution, and difficulties in post-modification functionalization, which also leads to the removal of beneficial nutrients[205]. Innovations such as metal–organic frameworks (for example, zirconium-based materials) and covalent organic frameworks are promising for non-dialysis UT elimination[206,207].

A deeper understanding of the metabolic pathways involved in UT production, as well as the enzymes and receptors responsible, opens up new avenues for specific therapeutics, for example, through the inhibition of specific pathways. Inhibition of trimethylamine (TMA) lyase and flavin-containing monooxygenase (FMO) by 3,3-dimethyl-1-butanol (DMB) and 3,3′-diindolyl methane show promise for reducing the production and detrimental effects of TMAO[208]. Inhibitors of microbial tryptophanase also have the potential to reduce IxS levels[209]. Additionally, inhibiting indoleamine-2,3-dioxygenase (IDO), kynureninase and the kynurenine pathway could limit harmful prothrombogenic downstream metabolites[140]. AHR inhibitors have shown potential in reducing thrombosis and improving angiogenesis in preclinical studies[122,123,210], although translating these results into humans is challenging owing to species differences in AHR function and gene regulation[211]. AHR also has a protective role in inflammation and gut integrity, necessitating careful consideration when developing AHR-targeted therapies.

Nutritional interventions

Food composition. The complex relationship between diet, gut microbiota and UT production, including their collective effect on CKD progression, is still being uncovered, with most knowledge stemming from metabolic-disease studies[212–214]. The longstanding nutritional recommendation of adopting a low-protein diet (LPD) to reduce uraemic symptoms and slow CKD progression[215,216] improves microbiota composition[217] and decreases precursors of UTs such as pCS, IxS and TMAO[218–220]. Two types of protein-restricted diets are recommended for CKD stages 3–5: an LPD providing 0.60–0.80 g/kg body weight/day and a very-LPD with 0.30–0.40 g/kg body weight/day, supplemented with 7–15 g/day of α-ketoacids[215]. However, the specific effect of α-ketoacids on gut microbiota and UT production remains unclear, despite preclinical data suggesting a beneficial effect on gut microbiota composition and the production of TMAO and IxS[221]. The protein source is also crucial — plant-based diets, rich in fibre, improve intestinal transit time, reduce colonic amino-acid breakdown into toxins and their precursors, and promote the production of beneficial intestinal metabolites (for example, SCFAs)[218]. In the short term, small RCTs have shown that increasing plant food diversity is practical and promotes a gut microbiome shift towards greater SCFA production and reduced UT levels, particularly in people with high baseline UT levels[222]. Similar effects have been reported in people receiving dialysis[223]. Although direct long-term data on UT reduction are lacking, several observational

studies and one RCT support associations between plant-based diets, slower eGFR decline and reduced mortality[224–226]. Tryptophan-derived metabolite production is probably driven more by substrate availability than bacterial abundance, with fermentable fibres reducing indole levels by inhibiting tryptophanase expression in *Escherichia coli* and promoting the production of beneficial metabolites by *Clostridium sporogenes*[136].

Additionally, improving dysbiosis through diet might reduce the intestinal absorption of UTs and their precursors by enhancing gut barrier integrity[227]. The type of ingested amino acids also has a key role. Reducing aromatic amino acids in the diet had nephroprotective effects in CKD mice by lowering pCS and IxS levels, similar to the effects of an LPD[228]. A diet high in sulfur-containing amino acids increases bacterial production of hydrogen sulfide, which can inhibit tryptophanase activity and reduce IxS production[229]. However, a large observational study with over 250 people receiving haemodialysis found no significant effect of dietary patterns on gut microbiota composition or UT levels[230].

Rather than focusing on individual nutrients, a holistic, food-based approach that considers all nutrients and incorporates the concept of the foodome (that is, the food-intrinsic metabolome) is needed[231]. This approach enables a better understanding of the effects of food additives, preservation methods, cooking processes and bioactive compounds on gut microbiota composition and intestinal-wall permeability. Emerging evidence highlights the negative effect of ultra-processed foods and additives on gut-derived metabolic production, although their specific impact on CKD still needs to be evaluated[232].

From a practical standpoint, based on current observational and experimental evidence, the most feasible and potentially effective dietary approach to reducing gut-derived UTs is a plant-based diet with moderate protein restriction (0.6–0.8 g/kg/day). Although stricter protein limitation or targeted amino-acid modulation might have theoretical benefits, they are difficult to implement owing to adherence issues and the risk of protein energy wasting. The relative contribution of protein source versus other lifestyle factors remains notably unclear and warrants further investigation. A diverse plant-based diet with moderate protein restriction thus appears both realistic and promising for future RCTs targeting UT reduction in CKD.

Biotics. Several studies suggest that probiotics and prebiotics might reduce UTs by directly affecting the gut microbiota[233,234]. However, multiple meta-analyses and systematic reviews of clinical studies in people with CKD have reported inconsistent results regarding their efficacy in improving kidney function or reducing UT levels and related outcomes, and highlighted the limited number of well-designed trials and the small study-sample sizes[235–239]. The inconsistent observations might be due to the random selection of strains and/or factors defining strain selection, such as the potential of some microbiota to express urease, subsequently increasing ammonia production or the selection of strains that do not thrive under uraemic conditions. Similarly, given the beneficial effects of indoles on the intestinal barrier, probiotics not promoting this activity could be detrimental. Regulatory guidelines now emphasize careful strain selection for efficacy and safety[240]. Additionally, ensuring compatibility between the probiotics and prebiotics used to formulate synbiotics is crucial, as interactions can vary depending on the prebiotic used. Promising strains, such as *Faecalibacterium prausnitzii*, *Lactobacillus casei* and *Lactobacillus paracasei*, have shown potential in reducing UTs and protecting kidney function[241–243]. Despite these promising results, whether healthy diets that include bioactive nutrients and biotic supplementation, and that can reduce UT production effectively, lead to improved long-term outcomes in CKD remains unclear.

Extracorporeal uraemic toxin removal

Although dialysis significantly prolongs the life of people with kidney failure, it does not adequately address the uraemic condition. Despite the use of diffusion and convection to advance dialysis, challenges remain. Traditional dialysis methods, including haemodialysis, haemodiafiltration (HDF) and peritoneal dialysis, cannot clear PBUTs efficiently owing to their high protein-binding properties and the absence of a secretion mechanism similar to that of healthy kidneys[244]. Continuous-flow peritoneal dialysis shows promise in enhancing solute clearance compared with conventional peritoneal dialysis, but current data are insufficient to draw firm conclusions, especially on long-term effects[245]. Larger dialysers with higher dialysate-flow rates or extended sessions, such as those used in nocturnal haemodialysis, have improved PBUT clearance, but not necessarily quality of life[246]. The CONVINCE study showed that high-volume HDF improves overall survival in cases where exchange volumes of >23 l per session are reached, as imposed by the study protocol. However, this survival benefit might be unrelated to better PBUT removal[247] given that previous studies suggest that convection has minimal effect on PBUT clearance, as it is primarily influenced by residual kidney function and tubular secretion[248,249]. Novel dialyser membranes have been developed with a higher median pore size and a narrower pore-size range, allowing more efficient removal of large toxins, without increasing transmembrane albumin losses (medium cut-off dialysers)[250]; these membranes enable overall PBUT removal similar to that achieved with HDF[251]. However, to the best of our knowledge, no hard outcome studies have demonstrated the superiority of this approach compared with standard dialysis or its non-inferiority versus high-volume HDF.

One key element hampering UT removal by dialysis is the intermittent nature of the treatment, given the multicompartmental distribution of UTs. A decrease in plasma concentration is relatively easy to obtain, but UT removal from extraplasmatic compartments is slower, resulting in rebound at the end of dialysis. Longer dialysis sessions favour removal from extraplasmatic compartments[252].

Emerging research and therapies

UT research is important, not only for people with CKD but also for other fields of research and clinical medicine. Given that AHR is activated by tryptophan-derived UTs, a better understanding of the various pathways controlled by AHR in CKD could also help to elucidate pathology linked to other hazardous AHR ligands, such as environmental pollutants[253]. In addition to tryptophan, numerous other ligands are present in the organism and the environment; thus, future research must focus on the identification of receptors for other toxins, as well as the pathways modulated by the activation or inhibition of those receptors, and their potential differences across cell types. Analysis of single-cell RNA sequencing data from experimental models of CKD could help to understand the effect of UTs at the molecular level in different organs. For in vitro approaches, standardization of solute concentrations, control conditions and cell types to be studied is crucial. An emerging concept in toxicology — the cocktail effect — postulates that a combination of low-concentration intoxicants or pollutants might lead to different and often more deleterious effects than single exposures; such an effect might also apply to UTs.

Early translation of basic UT research into clinical applications can initially be done on mouse models of CKD but, similar to in vitro

approaches, standardization is required. In addition to animal models, the 3Rs principle (replacement, reduction and refinement) dictates that non-animal-dependent models must be developed, such as those using organoids or organs-on-a-chip as advanced in vitro models. Finally, the ensuing knowledge must be confirmed in humans and implemented in the clinic with the support of large consortia of clinical researchers to generate big datasets of well-defined patient phenotypes at various stages of CKD, and a large array of biochemical data. Research and interdisciplinary collaboration in the field of UTs must be encouraged. With CKD estimated to become the fifth leading cause of death in the world[254] in 2050, identifying new therapeutic strategies that can reduce the burden of CKD by addressing uraemic toxicity is crucial; this field needs more basic, translational and clinical research.

Novel emerging therapies for kidney failure include portable or wearable artificial-kidney systems that offer patients more flexibility, mobility and autonomy than in-centre dialysis and might improve their quality of life. However, a major challenge for these systems is the continuous regeneration of a small volume of dialysate. Research into recycling systems based on sorbents might have great potential for dialysate regeneration, but this approach is still under preclinical investigation[255]. For specific removal of UTs, new dialysis membrane materials are currently under development. These include inorganic silicon-based polymers[256], polyvinylidene fluoride modified by coating with polyvinyl alcohol and chitosan-like material[257], or mixed-matrix membranes, such as a polyether sulfone–polyvinyl–pyrrolidone 90 composition with an extra layer consisting of activated carbon[258].

Given that only the free fraction of PBUTs is eliminated by dialysis, strategies that promote toxin dissociation from albumin could enhance clearance. Compounds such as warfarin, ibuprofen, tryptophan and lipids have been tested in vitro and small clinical studies to effectively displace PBUTs from albumin in both haemodialysis and peritoneal dialysis[259,260]. Current research focuses on selecting ideal competitors that block key albumin-binding sites, minimize side effects and optimize clearance pathways. Octanoate, a medium-chain fatty acid that does not exacerbate dyslipidaemia, effectively competes with PBUTs for binding to HSA and strikingly increases their removal[261]. Another interesting approach is the development of bioartificial kidney systems that could partly replace tubular secretory function by combining a cellular component with dialysis. Cells containing organic anion and cation transporters facilitate the clearance of PBUTs by displacing bound toxins from albumin and mediating the uptake of the toxins from the blood and their secretion into the dialysate. By combining an active secretory component (mimicking tubular function) with dialysis (mimicking glomerular filtration), an almost complete clearance of UTs would be anticipated to improve outcomes. Although promising, bioartificial kidney development still faces manufacturing, scalability and logistics challenges, which hamper its implementation[255].

Regarding gut microbiota manipulation, synthetic biology and omics technologies are being leveraged to develop engineered probiotics that enhance metabolic functions. Additionally, genetically modified probiotics are emerging as an extension of the traditional probiotic concept, enabling the delivery of therapeutic molecules. Such approaches have been tested in CKD, for example, deleting tryptophanase in *Bacteroides* to lower IxS levels[262] or modifying *Escherichia coli* to convert tyrosine into non-toxic metabolites[263].

In the long term, implantable devices that replace kidney function by using engineered tissues based on scaffolds, (stem) cells, and biological and mechanical triggers might be developed. This field of research is expanding rapidly, but generating vascularized, innervated and fully matured tissue with sufficient clearance capacity has not yet been possible[264,265].

To further advance knowledge in the field, future studies should apply methods for analysis of inter-organ communication and the damaging effects of URMs across organs in in vitro systems that contain multiple cell types, such as organs-on-a-chip or organoids, as well as preserving or restoring gut microbiome symbiosis and reducing UT (precursor) generation by the gut microbiome or systemic absorption into the circulation. The use of systems biology and in silico approaches[266] to predict clinical outcomes, such as inhibition of the harmful effects of AHR activation selectively, could enable therapeutic breakthroughs in the treatment of uraemic toxicity. The focus on biological interactions will require multidisciplinary and holistic efforts, including the integration of the ample multi-omics data gathered in the field of uraemic toxicity, to clarify interactions across organ systems. Finally, sophisticated machine-learning methods will be essential to advance diagnostic and therapeutic strategies in CKD, including their cost-effectiveness[267].

Conclusions

For a long time, uraemic toxicity research has focused solely on potentially toxic metabolites, treatment of their associated symptoms and their unspecific removal, probably hampering further improvements in patient outcomes. The introduction of a more standardized approach and novel analytical tools in UT research has enabled a more holistic approach. Untargeted analytical methods of detecting URMs can offer a balanced view on the potential interplay between toxic and beneficial metabolites involved in homeostasis and its imbalance in CKD. Improved insight into the transport of UTs over different barriers in the body and their direct or receptor-mediated effects; their role in inter-organ communication; the importance of PTMs in disrupting cellular processes and regulatory pathways; and increased awareness of the limitation and pitfalls of preclinical in vivo animal and in vitro models has largely extended our knowledge on the pathophysiology of uraemic toxicity. In addition, the search for UTs driving patient-reported outcome measures could help to improve patient quality of life[268,269]. However, our knowledge of demonstrated metabolic changes is far from sufficiently counteracted by currently available therapies, and a translation of this knowledge into novel therapies is urgently needed. Growing research insights into the origin of UTs, particularly gut-microbiota-derived UTs, combined with technological innovations in the field of dialysis, are enabling the identification of new therapeutic targets and improvements in UT removal, especially of PBUTs. Continued multidisciplinary and standardized research on uraemic toxicity is needed to explore newly discovered targets for intervention, with the aim of minimizing the burden of CKD in the lives of patients, from the early stages of disease.

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